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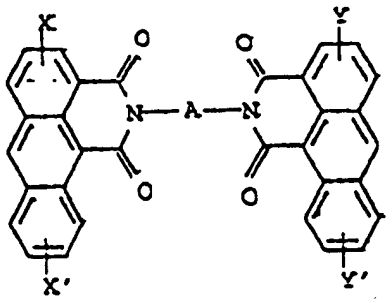
(54) Title: DIHYDRODIBENZO(DE,H)ISOQUINOLINES DERIVATIVES AND THEIR USE AS ANTI-CANCER AGENTS

(57) Abstract

Novel bis-1,2-dihydro-3H-dibenzisoquinoline-1,3-diones of formula (I), wherein X, X', Y and Y' are identical or different and are each H, NO_2, NH_2, C_1-C_6-alkylamino, di-C_1-C_6 alkylamino, NH-C_1-C_6-acyl, OH, C_1-H_6-alkoxy, halogen trihalomethyl, C_1-C_6-alkyl, formyl, C_1-C_6-alkylcarbonyl, ureyl, C_1-C_6-alkylureyl and A is a C_4-C_{12}-bridge which is interrupted at one, two or three points by a secondary or tertiary amino group, where two nitrogen atoms may additionally be bonded to one another by a C_1-C_4-alkylene group or a salt thereof with a physiologically tolerated acid. Processes for their preparation, pharmaceutical compositions containing them and methods of using them to treat malignancies, mainly human solid tumor carcinomas.



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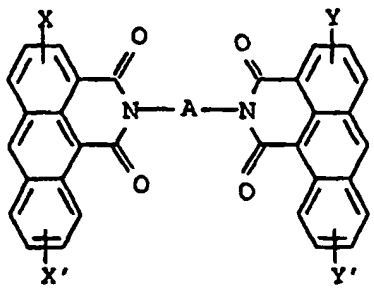
Dihydrodibenzo(de,h) isoquinolines derivatives and their use as anti-cancer agents

Description

This invention relates to novel bis-1,2-dihydro-3H-dibenzisoquinoline-1,3-diones and their salts, processes for their preparation, pharmaceutical compositions containing them and methods of using them to treat malignancies, mainly human solid tumor carcinomas.

The use of bis-naphthalimides for the treatment of tumor carcinomas is already known (see e.g. US 4,874,883, US 5,986,059 and DE 4,232,739). Further, dibenzisoquinolines have been described (EP 536,208) which have anti-cancer activity.

The present invention relates to bis-1,2-dihydro-3H-dibenzisoquinoline-1,3-diones of the formula I



I,

wherein X, X', Y, and Y' are identical or different and are each H, NO_2, NH_2, C_1-C_6-alkylamino, di-C_1-C_6 alkylamino, NH-C_{1-6}-acyl, OH, C_1-H_6-alkoxy, halogen, trihalomethyl, C_1-C_6-alkyl, formyl, C_1-C_6-alkylcarbonyl, ureyl, C_1-C_6-alkylureyl and A is a C_4-C_{12}-bridge which is interrupted at one, two or three points by a secondary or tertiary amino group, where two nitrogen atoms may additionally be bonded to one another by a C_{1-4}-alkylene group and the salts thereof with physiologically tolerated acids.

One class of compounds of the present invention is bis-1,2-dihydro-3H-dibenzisoquinoline-1,3-diones of the formula I in which at least one of X, X', Y, and Y' are not H, i.e., wherein X, X', Y, and Y' are identical or different and are selected from the group consisting of NO_2, NH_2, NH-lower acyl, C_{1-6}-alkylamino, di-C_{1-6}-alkylamino, OH, C_{1-6}-alkoxy, halogen, trihalomethyl, C_{1-6}-alkyl, formyl, C_{1-6}-alkylcarbonyl, ureyl, and C_{1-6}-alkylureyl.

It is currently preferred in various embodiments of this class for none of X, X', Y, and Y' to be NO_2.

One subclass of the foregoing is bis-1,2-dihydro-3H-dibenzoisoquinoline-1,3-diones of the formula I wherein at least one of X, Y', Y and Y' is NH_2, NH-lower acyl, C_{1-6}-alkylamino or di-C_{1-6}-alkylamino. This class includes, among others, compounds of the formula I in which X and Y are H; X' and Y' are $NHCOCH_3$; and -A- is $-CH(CH_3)-CH_2-NH-CH_2-CH_2-NH-CH_2-CH(CH_3)-$ or $-(CH_2)_2-NH-(CH_2)_3-NH-(CH_2)_2-$.

Another class of compounds of the present invention is bis-1,2-dihydro-3-H-dibenzisoquinoline-1,3-diones of the formula I in which A is

$$C_n\text{-}NR\text{-}C_{n'} \quad \text{or} \quad C_n\text{-}NR\text{-}C_{n''}\text{-}NR'\text{-}C_{n'}$$

wherein C_n, $C_{n'}$, and $C_{n''}$ are identical or different and are each C_{1-4}-alkylene radicals and R and R'are H, C_{1-4}-alkyl, benzyl, phenyl, or phenyl substituted by a halogen atom or a C_{1-4}-alkyl group or an amino group.

One subclass of such compounds is bis-1,2-dihydro-3H-dibenzoisoquinoline-1,3-diones of the formula I wherein the bridging moiety A joining the two ring systems is:

$$-CH_2-CH_2-NR-CH_2-CH_2-NR'-CH_2-CH_2$$

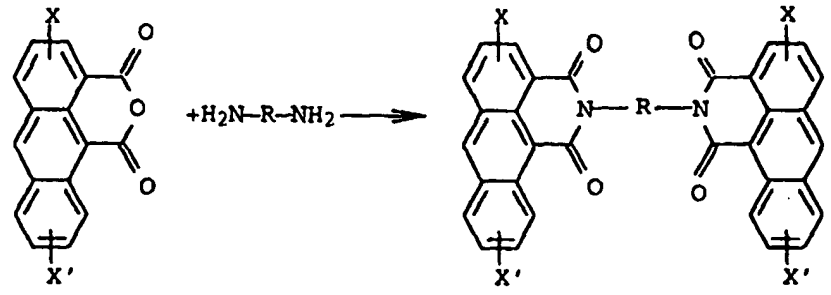
or

$$-CH_2-CH_2-NR-CH_2-CH_2-CH_2-NR'-CH_2-CH_2$$

wherein R and R' are as previously defined. These compounds include those in which X and X' and R and R' are all H.

Compounds I of the present invention can be synthesized according to the following methods:

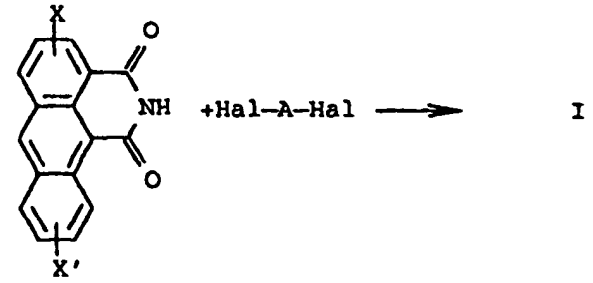
1. by reacting an anthracene-1,9-dicarboxylic anhydride of the formula II with a polyamine of the formula III:



II III I

Instead of the acid anhydride the corresponding dicarboxylic acid or dicarboxylic acid halide may be used;

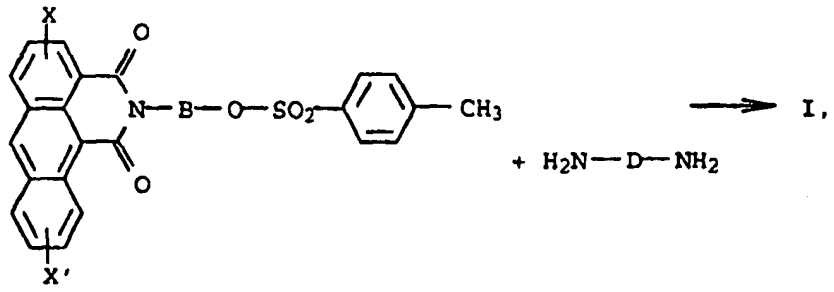
2. by reacting an anthracene-1,9-dicarboxylic amide VI with a compound of the formula VII:



VI VII

wherein Hal means a halogen atom, preferably bromine;

3. - if A is interrupted by two nitrogen atoms - by reacting a compound of the formula IV with a diamine of the formula V:



IV V

wherein B plus D are alkylene residues so that 2 B plus D contain 4 to 12 carbon atoms.

Reaction 1 is performed by reacting the compound II with a half equivalent of a polyamine of the formula III in an organic solvent such as alcohols (especially ethanol), acetone, DMSO, THF, DMF, dioxane, aromatic hydrocarbons (especially toluene), or any inert solvent. The temperature of the reaction should be between -20°C and the boiling temperature of the solvent. Fairly high temperatures are preferred.

Reactions 2 and 3 are performed under the same conditions, but in the presence of a base.

The final product is filtered off or the reaction mixture is evaporated to dryness under reduced pressure and the residue is purified in conventional manner by crystallization or chromatography.

The starting compounds II-VI can be prepared by methods known from the literature, or they are commercial products.

The bis-1,2-dihydro-3H-dibenzoisoquinoline-1,3-diones so obtained are used per se, or they can be acidified with the appropriate mineral or organic acid to produce a pharmaceutically acceptable salt, e.g. the methanesulfonate or the acetate salt, which can be recovered by filtration. Salts of the free base can also be prepared by acidifying a suspension of the free base in ethyl alcohol, dichloromethane, ether, etc. with the appropriate mineral or organic acid and collecting by filtration the solid thus formed.

Other acids for salt formation are known from the art, see e.g., Brafia et al., U.S. Patent 4,874,883.

The present invention further encompasses pharmaceutical compositions containing a tumor-inhibiting compound according to the invention together with a pharmaceutically acceptable carrier. It also relates to methods for treating tumors in mammals comprising administration of a tumor-inhibiting amount of a compound according to the invention to a mammal with such a tumor. The compounds according to the invention may be formulated into pharmaceutical compositions and administered to patients using conventional materials and methods such as are described in Brafia et al., US 4,874,883 and US 5,206,249 (the contents of both of which are hereby incorporated herein by reference). See especially US 5,206,249 at column 22, line 10 through the end of column 23.

The compounds according to the invention have cytotoxic activity useful in the treatment of various cancers. These compounds can be evaluated for relative efficacy in *in vitro* and *in vivo* models such as are generally accepted in this art, including those described in US 5,206,249 (see especially column 19 to column 22, line 9). Efficacy in such models is indicative of utility in the treatment of solid tumors in human patients and evidences important therapeutic utility in the treatment of cancer, particularly solid tumor carcinomas, such as colon carcinoma, breast tumors, prostate cancer, and non-small lung carcinoma. The new compounds exhibit better properties than prior art compounds with regard to activity, toxicity and/or solubility.

A. *In vitro* methodology

Cytotoxicity may be measured using standard methodology for adherent cell lines such as the microculture tetrazolium assay (MTT). Details of this assay have been published Cancer Research 48:589-601, 1988). Exponentially growing cultures of tumor cells such as the HT-29 colon carcinoma or LX-1 lung tumor are used to make microtiter plate cultures. Cells are seeded at 5000-20,000 cells per well in 96-well plates (in 150 µl of media), and grown overnight at 37°C. Test compounds are added, in 10-fold dilutions varying from 10^{-4} M to 19^{-10} M. The cells are then incubated for 48-72 hours. To determine the number of viable cells in each well, the MTT dye is added (50 µl of 3 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide in saline). This mixture is incubated at 37°C for 5 hours, and then 50 µl of 25% strength SDS (pH 2) is added to each well. After overnight incubation, the absorbance of each well at 550 nm is read using an ELISA reader. The values for the mean +/- SD of

data from quadruplicate wells are calculated, using the formula % T/C (% cells treated/control).

$$\frac{\text{OD of treated cells}}{\text{OD of control cells}} \times 100 = \% \text{ T/C}$$

The concentration of test compound which gives a T/C of 50% growth inhibition is designated as the IC_{50}.

B. *In vivo* methodology

Compounds according to the invention may be further tested in any of the various preclinical assays for in vivo activity which are indicative of clinical utility. Such assays may be conducted with nude mice into which tumor tissue, preferably of human origin, has been transplanted ("xenografted"), as is well known in this field. Test compounds are evaluated for their antitumor efficacy following administration to the xenograft-bearing mice.

More specifically, human tumors which have been grown in athymic nude mice are transplanted into new recipient animals, using tumor fragments which are about 50 mg in size. The day of transplantation is designated as day O. Six to ten days later, mice are injected intravenously or intraperitoneally with the test compounds, in groups of 5-10 mice per dose. The compounds are administered daily for 5 days, 10 days or 15 days, at doses from 10-100 mg/kg body weight. Tumor volumes are calculated using the diameters measured twice weekly. Tumor volumes whose diameters are measured with Vernier calipers are calculated by the formula:

$$(\text{length} \times \text{width}^2)/2 = \text{mm}^3 \text{ (tumor volume)}.$$

Mean tumor volumes are calculated for each treatment group, and T/C values determined for each group relative to the untreated control tumors. The data may be evaluated as follows. A T/C value of 1.0 or greater indicates that the compound had no effect on tumor growth, while values < 1.0 indicate some reduction in tumor mass. Values of 0.15-0.49 may be considered to reflect moderate activity, < 0.01-0.14 good to excellent activity. Outstanding activity indicates a compound which provides complete regression of tumor material (no visible tumor mass following therapy). Compounds yielding T/C values > 0.50 are considered inactive.

The invention can be further understood by referring to the following examples, in which parts and percentages are by weight unless otherwise specified.

Example 1

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinoline-2-yl)ethyl]-1,3-propanediamine

A mixture of 1.6 g (6 mmol) of anthracene-1,9-dicarboxylic anhydride in 40 ml of toluene was treated with 0.5 g (3 mmol) of N,N'-bis(2-aminoethyl)-1,3-propanediamine dissolved in 10 ml of toluene. The mixture was refluxed for 4 h and then filtered. The solution was allowed to cool and the solid formed was filtered, washed, dried and recrystallized from toluene. 0.93 g (50%) of N,N'-bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine were obtained. M.p. 191°C (toluene). ^{1}H-NMR ($CDCl_3$) δ = 1.84 (q, 2H, J = 6 Hz, $-CH_2-$); 2.74 (broad,s, 2H, NH); 2.89 (t, 4H, J = 6 Hz, CH_2); 3.02 (t, 4H, J = 6Hz, CH_2); 4.31 (t,4H, J = 6 Hz, CH_2); 7.54 (m, 4H, H-5 and H-9); 7.73 (m, 2H,H-10); 7.89 (d, 2H, J = 8 Hz, H-8); 8.22 (d, 1H, J = 8 Hz, H-4); 8.51 (s,2H, H-7); 8.57 (d, 2H, J = 8 Hz, H-6); 9.78 (d,2H, J = 8 Hz, H-11) p.p.m.. Anal. Calculated for $C_{39}H_{32}N_4O_4$: C 75.46; H 5.19; N 9.02. Found: C 75.14; H 5.37; N 8.78. Acetate m.p. 155°C. Methanesulfonate m.p. 243°C.

Example 2

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,2-ethylenediamine.
As example 1. Yield 66%. M.p. 203°C (DMF-H_2O)

Example 3

N,N'-Bis[3-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)propyl]-1,4-butanediamine.
As example 1. Yield 46%. M.p. 183°C (toluene).

Example 4

[3-(1,2-dihydro-1,3-dioxo-3,4-dibenz[de,h]isoquinolin-2-yl)propyl][4-(1,2-dihydro-1,3-dioxo-3,4-dibenz[de,h]isoquinolin-2-yl)butyl]amine.
As example 1. Yield 41%. M.p. 244°C (DMF).

Example 5

N,N'-Bis[2-1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,4-butanediamine.
As example 1. Yield 40%. M.p. 179°C (toluene).

Example 6

Bis[3-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)propyl]methylamine.
As example 1. Yield 35%. M.p. 194°C (toluene).

Example 7

Bis [3-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)propyl]amine.
As example 1. Yield 83%. M.p. 184°C (toluene).

Example 8

[2-(1,2-Dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl][3-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)propyl]amine.
As example 1. Yield 78%. M.p. 260°C (DMF).

Example 9

Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl)amine.
As example 1. Yield 53%. M.p. 271°C (DMF-H_2O).

Example 10

N,N'-Bis[3-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)propyl]-1,2-ethylenediamine.
As example 1. Yield 61%. M.p. 180°C (toluene).

Example 11

N,N'-Bis[3-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)propyl]-1,3-propanediamine.
As example 1. Yield 41%. M.p. 140°C (toluene).

Example 12

N,N'-Bis[1,2-dihydro-8-nitro-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]1,3-propanediamine.
As example 1. Yield 52%. M.p. >340°C (toluene)

Example 13

N,N'-Bis-[2-(1,2-dihydro-8-nitro-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]1,3-ethylenediamine.
As example 1. Yield 57%. M.p. >340°C (toluene)

Example 14

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-N,N'-dimethyl-1,2-ethylenediamine.

As example 1. Yield 77%. M.p. 255°C (toluene).

Example 15

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,5-pentanediamine.

As example 1. Yield 25%. M.p. 122°C (toluene).

Example 16

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]hexahydropirimidine.

A mixture of 0.5 g (0.8 mmol) of N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine and 1 ml of 36% formaldehyde in 100 ml of ethanol was refluxed for 7 hours. The solid was filtered, washed, dried, and recrystallized from toluene. 0.3 g (58%) of N,N'-bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]hexahydropirimidine were obtained. M.p. 222°C (toluene).

Example 17

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine

A mixture of 1.47 g (5 mmol) of anthracene-1,9-dicarboxylic acid dimethyl ester in 50 ml of toluene is treated with 0.4 g (2.5 mmol) of N,N'-bis(2-aminoethyl)-1,3-propanediamine in 20 ml of toluene. The suspension is refluxed for 24 hours and then cooled to room temperature. The solid is filtered, dried, and crystallized from toluene to give 0.65 g (42%) of N,N'-bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]-isoquinolin-2-yl)ethyl]-1,3-propanediamine. M.p. 191°C.

Example 18

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine

0.4 g (2.5 mmol) of N,N'-bis(2-aminoethyl)-1,3-propanediamine in 20 ml of toluene are added to a mixture of 1.51 g (5 mmol) of anthracene-1,9-dicarboxylic acid dichloride in 50 ml of toluene. The suspension is refluxed for 20 hours and then cooled to room temperature. The solid is filtered, dried and crystallized from toluene to give 0.54 g (35%) of N,N'-bis[2-(1,2-dihydro-1,3-dioxo-3H-di-benz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine. M.p. 191°C.

Example 19

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine

A. 2-(2-Hydroxyethyl)-1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione

A mixture of 1.51 g (6 mmol) of anthracene-1,9-dicarboxylic acid anhydride and 0.4 g (6.5 mmol) of ethanolamine in 50 ml of toluene is refluxed for 5 hours and then cooled to room temperature. The solid is filtered, dried and crystallized from toluene to give 1.5 g (85%) of 2-(2-hydroxyethyl)-1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione. M.p. 211°C.

B. 2-[2-(p-Toluenesulfonyloxy)ethyl]-1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione

A mixture of 1.01 g (3.5 mmol) of 2-(2-hydroxyethyl)-1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione in 10 ml of pyridine is treated with 0.69 g (3.6 mmol) of p-toluenesulfonyl chloride. The mixture is stirred at room temperature for 24 hours and poured into 50 ml of cold water. The solid is collected, washed with water, dried in vacuo, and crystallized from dimethylformamide water to give 1.2 g (77%) of 2-[2-(p-toluenesulfonyloxy)ethyl]1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione. M.p. 240°C.

C. N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine

A mixture of 2.2 g (5 mmol) of 2-[2-(p-toluenesulfonyloxy)ethyl]-1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione, 0.4 g (2.5 mmol) of 1,3-propanediamine in 200 ml of acetonitrile is refluxed in the presence of 0.6 g (5.6 mmol) of sodium carbonate for 24 hours. The reaction mixture is concentrated in vacuo. The residue is treated with water (100 ml) and extracted with dichloromethane. The organic layers are combined, dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue is chromatographed, eluting with dichloromethane, methanol, acetic acid (80:15:5). The appropriate fractions are combined, concentrated in vacuo and crystallized from toluene to give 0.3 g (20%) of N,N'-bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine. M.p. 191°C.

Example 20

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine

A. 1,2-Dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione

1.51 g (6 mmol) of anthracene-1,9-dicarboxylic acid anhydride was treated with 10 ml of ammonium hydroxide (28 %). After refluxing for 16 hours the solid was collected, washed with water, dried in vacuo, and crystallized from dimethylformamide-water to give 1.3 g (86%) of 1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione. M.p. 310°C.

B. N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine

A mixture of 1.23 g (5 mmol) of 1,2-dihydro-3H-dibenz[de,h]isoquinoline-1,3-dione in 100 ml of ethanol is treated with 280 mg (5 mmol) of potassium hydroxide in 50 ml of ethanol. After refluxing for 3 hours, 0.65 g (2.5 mmol) of N,N'-bis(2-bromoethyl)-1,3-propanediamine in 50 ml of ethanol are added and the whole is refluxed for 24 hours. The reaction mixture is concentrated in vacuo. The residue is treated with water (100 ml) and extracted with dichloromethane. The organic layers are combined, dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue is chromatographed, eluting with dichloromethane, methanol, acetic acid (0:15:5). The appropriate fractions are combined, concentrated in vacuo and crystallized from toluene to give 0.31 g (20%) of N,N'-bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine.
M.p. 191°C.

Example 21

N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine

A. N-[2-(1,2-Dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-N'-(2-aminoethyl)-1,3-propanediamine

A solution of 5.0 g (31 mmol) of N,N'-bis(2-aminoethyl)-1,3-propanediamine in 200 ml of ethanol 99% is treated with 1,5 g (6 mmol) of anthracene-1,9-dicarboxylic acid anhydride in 100 ml of ethanol and stirred for 24 hours at room temperature. The solid is collected on a filter, washed with ethanol and crystallized from ethanol to give 0.5 g (20%) of N-[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-N'-(2-aminoethyl)-1,3-propanediamine.
M.p. 150°C.

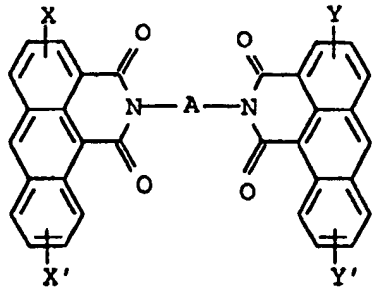
B. N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine

A mixture of 1.0 g (2,5 mmol) of N-[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-N'-(2-aminoethyl)-1,3-propanediamine in 50 ml of toluene was treated with 0.62 g (2,5 mmol) of anthracene-1,9-dicarboxylic acid anhyride in 10 ml of toluene, refluxed for 6 hours, and coo-

led to room temperature. The solid was collected, dried in vacuo, and crystallized from toluene to give 0.8 g 48% of N,N'-Bis[2-(1,2-dihydro-1,3-dioxo-3H-dibenz[de,h]isoquinolin-2-yl)ethyl]-1,3-propanediamine. M.p. 191°C.

Claims

1. A compound of the formula



I,

wherein X, X', Y, and Y' are identical or different and are each H, NO_2, NH_2, C_1-C_6-alkylamino, di-C_1-C_6 alkylamino, NH-C_{1-6}-acyl, OH, C_1-H_6-alkoxy, halogen, trihalomethyl, C_1-C_6-alkyl, formyl, C_1-C_6-alkylcarbonyl, ureyl, C_1-C_6-alkyl-ureyl and A is a C_4-C_{12}-bridge which is interrupted at one, two or three points by a secondary or tertiary amino group, where two nitrogen atoms may additionally be bonded to one another by a C_{1-4}-alkylene group or a salt thereof with a physiologically tolerated acids.

2. A bis-1,2-dihydro-3H-dibenzisoquinoline-1,3-dione as claimed in claim 1 where X, X', Y and Y' are hydrogen.

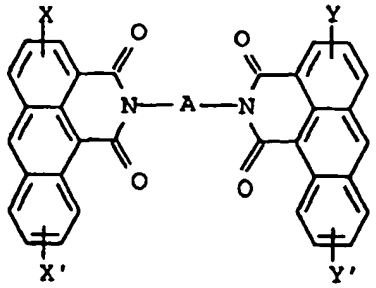
3. A bis-1,2-dihydro-3H-dibenzisoquinoline-1,3-dione as claimed in claim 1 as a salt of acetic or methanesulfonic acid.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as claimed in claim 1.

5. A method of treating tumors in humans comprising administering to the patient with such tumor a tumor-inhibiting amount of a compound as claimed in claim 1.

6. The method of preparing a compound of the formula I according to claim 1, where

1. an anthracene-1,9-dicarboxylic acid anhydride of the formula I

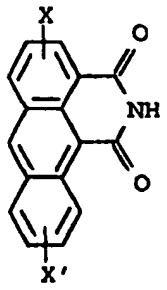


I,

or the corresponding free acid or acid halide, is reacted with a compound of the formula II

$H_2N\text{-}A\text{-}NH_2$ II or

2. an anthracene-1,9-dicarboxylic amide VI



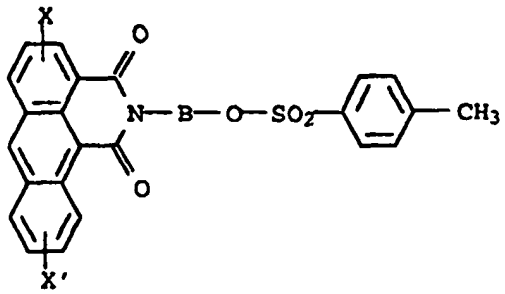
VI

is reacted with a compound of the formula VII

Hal-A-Hal VII,

wherein Hal is a halogen atom or

3. - if A is interrupted by two nitrogen atoms - a compound of the formula IV



IV

is reacted with a diamine of the formula V

$$H_2N\text{-}D\text{-}NH_2 \quad V,$$

wherein B plus D are alkylene radicals so that 2 B plus D contain 4 to 12 carbon atoms.

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/EP 95/01347

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/18 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 00281 (RESEARCH CORPORATION TECHNOLOGIES INC.) 9 January 1992 cited in the application see claims 1-13,16,17 ---	1-6
Y	EP,A,0 125 439 (WARNER-LAMBERT COMPANY) 21 November 1984 see claims ---	1-6
Y	EP,A,0 281 902 (KNOLL AG) 14 September 1988 see claims ---	1-6
Y	WO,A,94 06771 (RESEARCH CORPORATION TECHNOLOGIES INC.) 31 March 1994 see claims --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 1995	16.06.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/EP 95/01347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 6, 19 March 1993 WASHINGTON US, pages 765-770, SALAH M. SAMI ET AL '2-Substituted 1,2-dihydro-3H-dibenzo[de,h]isoquinoline-1 ,3-diones.A new class of antitumor agent' see the whole document	1-6
A	DE,A,42 32 739 (KNOLL AG) 31 March 1994 cited in the application see claims	1-6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter tional application No.
PCT/EP 95/ 01347

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5
because they relate to subject matter not required to be searched by this Authority, namely:
Remark - Although claim 5 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna l Application No
PCT/EP 95/01347

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9200281	09-01-92	AU-B-	643539	18-11-93
		AU-A-	8050191	23-01-92
		EP-A-	0536208	14-04-93
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		US-A-	4665071	12-05-87
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		DE-A-	3881544	15-07-93
		ES-T-	2054716	16-08-94
		JP-A-	63230671	27-09-88
		US-A-	4874863	17-10-89
WO-A-9406771	31-03-94	AU-B-	5127893	12-04-94
		CA-A-	2144049	31-03-94
DE-A-4232739	31-03-94	CN-A-	1094036	26-10-94
		WO-A-	9407862	14-04-94